Serum IL-6 and IGF-1 improve clinical prediction of functional decline after hospitalization in older patients

Marie de Saint-Hubert[1], Jacques Jamart[2], Gabriel Morrhaye[3], Henri J. Martens[3], Vincent Geenen[3], Thi Kim Duy Vo[4], Olivier Toussaint[4] and Christian Swine[1]

[1]Department of Geriatrics and [2]Biostatistics, Cliniques Universitaires de Mont-Godinne, UC Louvain, [3]Centre d'Immunologie de Liège, University of Liège, [4]Laboratory of Cellular Biochemistry and Biology, University of Namur, Belgium

ABSTRACT. ***Background and aims:*** *Although inflammatory and hormonal markers have been associated with further functional adverse outcomes in community-dwelling seniors, these markers have not been studied from this perspective in acutely ill older patients. This prospective study was designed to determine whether biological markers can improve the predictive value of a clinical screening tool to assess the risk of functional decline in hospitalized older patients.* ***Methods:*** *Patients aged 75 years and over admitted for hip fracture, acute heart failure or infection (n=118) were recruited. The clinical screening tool SHERPA was filled in on admission, with concomitant measurement of interleukin-6 (IL-6), insulin-like growth factor 1 (IGF-1), C-reactive protein (CRP), white blood cells, urea, albumin, pre-albumin and total cholesterol. Functional decline was defined as a decrease of one point in the activities of daily living scale between pre-admission and 3-month post-discharge status. We compared the discrimination calibration of SHERPA* vs *SHERPA+, a logistic regression model including SHERPA and selected biomarkers.* ***Results:*** *Three months after discharge, functional decline had occurred in 46 patients. IL-6 and IGF-1 were selected, since their levels were significantly different between decliners and non-decliners, and were included in the new logistic regression model SHERPA+. Areas under the ROC curve [95% CI] for functional decline prediction were 0.73 [0.63-0.81] for SHERPA* vs *0.79 [0.69-0.86] for SHERPA+ (*p*=0.14). However, SHERPA+ was better calibrated, as the average predicted risk of functional decline within subgroups matched the proportion which actually underwent functional decline (Brier score=0.185). Since functional decline was higher in patients with hip fracture, the SHERPA+ model was challenged by including the diagnosis. Only SHERPA, IGF-1 and diagnosis were significantly associated with functional decline.* ***Conclusions:*** *Selected biological markers may marginally improve the clinical prediction of post-discharge functional decline in hospitalized patients, and may allow to stratify them appropriately. The predictive value of these biomarkers is not fully independent of disease status. Further studies are needed to confirm these results in a cohort representative of older patients admitted through the emergency department.*

(Aging Clin Exp Res 2011; 23: 106-111)

INTRODUCTION

Identification of elderly subjects at risk of functional decline is a major public health concern since targeted geriatric interventions may prevent or limit functional loss in both community-dwelling subjects and hospitalized patients (1, 2). Functional recovery after an acute health event may indeed contribute toward identifying frail older patients (3, 4).

In the hospital setting, several screening tools predicting functional decline after hospitalization have been proposed (5-7). A recent systematic review compared several of them and, since none had sufficient predictive validity, the authors recommended to test several other procedures to improve the predictive value of these instruments (8). Various physiological markers have been suggested as valuable candidates for this purpose (9, 10).

Key words: Functional decline, hospitalized elderly, IGF-1, IL-6, predictive value.

Correspondence: Marie de Saint-Hubert, MD, Cliniques Universitaires de Mont-Godinne, Service de Gériatrie, Avenue du Dr Therasse 1, B-5530 Yvoir, Belgium.
E-mail: marie.desainthubert@uclouvain.be

Received November 24, 2009; accepted in revised form May 4, 2010.
First published ahead of print May 6, 2010 as DOI: 10.3275/7028

Inflammation and neuroendocrine dysregulation have been proposed as impaired physiological mechanisms involved in the process of functional decline (11). In community-dwelling seniors, peripheral blood markers of inflammation, including interleukin-6 (IL-6), C-reactive protein (CRP) and albumin, have been independently correlated with functional adverse outcomes in several longitudinal cohort studies. Ferrucci et al. demonstrated a relationship between inflammation and the development of further disability in activities of daily living (ADL) (12, 13). In another study, a summary score including several peripheral blood markers of inflammation (IL-6, albumin, cholesterol, CRP) was associated with increased risk of functional decline at three years (14). Alterations in hormonal regulations have also been proposed as mediators of functional decline in older people. Insulin-like growth factor-1 (IGF-1) declines in normal aging (15) and is mainly regulated by nutritional status (16). According to Cappola et al., IL-6 and IGF-1 acted synergistically to promote disability and mortality (9).

However, few studies have investigated the potential interest of these biomarkers in hospitalized older patients. The aim of this study was to determine whether selected inflammatory and hormonal markers, measured early after admission, can improve the predictive validity of a clinical tool screening for the risk of functional decline following hospitalization of older patients.

METHODS

Participants

Participants were recruited among patients 75 years old and over, hospitalized in acute medical and surgical wards of a tertiary care university hospital, through the emergency department. To reduce heterogeneity and address specific models of inflammatory challenges, we selected patients with one of the following admission diagnoses: hip fracture after surgery, acute heart failure, or documented infection (with bacteriological and/or radiological proof). Patients were excluded if they had taken steroid or non-steroid anti-inflammatory drugs one week before inclusion, had cancer, had stayed in hospital within the previous two weeks, were admitted for intensive or palliative care, or were completely dependent in activities of daily living (ADL). Informed consent was obtained from each participant, or the caregiver when patients were unable to answer. The ethics committee of the hospital approved the study.

Data collection

Each participant was assessed within 72 hours of admission by two trained interviewers. In case of deafness, impaired cognitive status or institutionalization, questions were asked to the referent person (family member, nursing home staff). Functional status was assessed at baseline level (2 weeks before admission) with a modified Katz index of ADL (17). Each of the 6 ADL (bathing, dressing, transferring, toileting, being continent, eating) was rated 1 if the patient could perform the activity and 0 if the patient needed assistance. Comorbidity was rated with the Cumulative Rating Scale adapted for geriatrics (CIRS-G), which assesses 14 categories of organ systems (severity of impairment: 0 to 4; total score: 0-56; severity index= total score/number of categories: 0-4) (18). The risk of functional decline 3 months after discharge was assessed by SHERPA (*Score Hospitalier d'Evaluation du Risque de la Perte d'Autonomie*), a 5-item predictive tool including age, history of falls in the previous year, cognitive function, performance in instrumental ADL (iADL) 2 weeks before admission and self-rated health (5). Cognitive function was assessed with a shortened form of the Mini Mental Status Examination (21-item MMSE), excluding the 9 last items for practical reasons and distinguishing patients in 2 groups (<15/21 and ≥15/21) (19). The 7 iADL assessed were telephoning, using transportation, preparing meals, doing housework, taking medications and managing finances, and were rated 1 (independent) or 0 (needing assistance) (7 points) (20). SHERPA ranges from 0 to 11.5 (low to high risk of functional decline) and was chosen because it was developed in a comparable Belgian population and showed similar performance compared with other tools predicting functional decline (8).

Biological variables

Blood sample were taken after a 12-h overnight fast within 96 hours of admission, and were delivered to the central laboratory for measurement of C-reactive protein (CRP), white blood cells, urea, albumin, pre-albumin and total cholesterol. Aliquots were stored at -80°C until analysis. Interleukin-6 and IGF-1 were measured in duplicate by an enzyme-linked immunosorbent assay (ELISA) (Biosource, Nivelles, Belgium). The minimal detectable concentrations for IL-6 and IGF-1 were respectively 2 pg/mL and 4.9 ng/mL.

Outcomes

Functional status was reassessed 3 months after discharge by phone contact, and functional decline was defined as a loss of at least 1 point on the ADL scale between premorbid status (2 weeks before admission) and 3-month post-discharge evaluation.

Statistical analysis

Comparisons between groups used the chi-square test for categorical variables and the Wilcoxon rank sum test for numerical variables. Each individual biological variable (CRP, white blood cells, urea, albumin, pre-albumin, total cholesterol, IL-6 and IGF-1) was tested in a logistic regression model including SHERPA. We assessed the accuracy of the predictive models in two ways. Discrimination

– the ability to separate patients with or without disease – was measured by the area under the receiver operating characteristic (ROC) curve. ROC curves were compared with the Hanley and McNeil method (21). Calibration – the ability of the model to estimate the probability of a future event correctly – was measured by comparing the average predicted probability of the event in subgroups with the observed proportion developing the event within those subgroups. We created four subgroups, with quartiles of estimated risk of functional decline (0 to <25%, 25 to <50%, 50 to <75%, 75 to 100%). These subgroups were determined both for SHERPA and the model including SHERPA and biomarkers. For each subgroup, mean predicted and mean actual functional decline rates were calculated. The quality of calibration was assessed by computing the Brier score, in which 0 implies perfect prediction and 1 represents no predictive value (22).

The impact of primary medical diagnosis was also tested in the logistic regression model including SHERPA.

Statistical analyses were performed by SPSS 15.0 software (SPSS Inc., Chicago, (Il), and ROC curves were graphed by MedCalc 9.4 software (MedCalc, Mariakerke, Belgium).

RESULTS

Patient characteristics

One hundred and eighteen patients were included. Within 3 months of hospital discharge, 17 patients had died. Since functional data at follow-up were missing for three patients, 98 patients were included in the analyses (mean age 81.8±5.2 yrs, 57% women, 16 resident in nursing homes). The distribution of patients according to the 3 selected diagnoses was: 31 with heart failure, 32 with hip fracture, and 35 with documented infection. The median length of stay was 12 days [interquartile range, IQ 8-19 days]. Three months after discharge, functional decline had occurred in 46 patients (47%). Table 1 lists baseline patient characteristics according to the presence or absence of functional decline at 3 months. Patients with functional decline were 3 years older than those who maintained functional status (p=0.002), and had poorer pre-admission functional status (ADL and IADL). There were no significant differences in gender or comorbidity. The median length of stay was significantly higher in patients who presented functional decline at follow-up (13 days [IQ 10-24] *vs* 11 days [IQ 7.5-17], p=0.046). The rate of functional decline was sig-

Table 1 - *Baseline characteristics of study population.*

	Functional decline 3 months after discharge		*p*-value
	Yes n= 46	**No n= 52**	
Clinical characteristics			
Age (mean±SD)	83.6±5.6	80.2±4.3	0.002
Sex (% female)	65	50	ns
Comorbidity (CIRS-G), mean±SD			
Total score	13.7±4.4	12.2±4.3	ns
Severity index	2.3±0.3	2.3±0.4	ns
Primary medical diagnosis, n (%)			<0.001
Hip fracture	24 (75)	8 (25)	
Heart failure	11 (35)	20 (65)	
Infection	11 (31)	24 (69)	
ADL, mean±SD	3.5±2.1	4.4±1.6	0.042
IADL, mean±SD	2.9±2.5	4.2±2.2	0.009
MMSE (/ 21), mean±SD	14.3±4.7	16.7±4.8	0.001
SHERPA (0-11.5), mean±SD	7.1±2.6	4.7±2.7	<0.001
Biological values, median (interquartile range)			
CRP, mg/dL	11.7 (6.5-16.2)	9.8 (2.9-19.2)	ns
Leucocytes, nbr/µL	8595 (7280-11780)	8615 (6765-10165)	ns
Urea, mg/dL	44 (32-60)	43 (34.5-62)	ns
Clearance, mL/min	46.6 (32.1-68.1)	50.0 (34.4-72.3)	ns
Albumin, mg/dL	3083 (2605-3401)	3347 (2998-3595)	ns
Pre-albumin, mg/dL	13 (10-14)	14 (11-20)	ns
IL-6, pg/mL	98.6 (52.8-208.9)	60.4 (29.6-133.6)	0.019
IGF-1, ng/mL	155.5 (96.9-241.6)	204.2 (166.2-270.5)	0.002

CIRS-G: Cumulative Illness Rating Scale adapted for Geriatrics; ADL: activities of daily living; IADL: Instrumental ADL; MMSE: Mini Mental State Examination; SHERPA: Score Hospitalier d'Evaluation du Risque de la Perte d'Autonomie.

Table 2 - *Functional trajectories according to admission diagnosis.*

Admission diagnosis	ADL (mean±SD)			
	Pre-morbid	Admission*	Discharge*	3-month*
Heart failure (n=31)	4.4±1.7	3.6±2.1	4.0±1.9	4.1±1.9
Infection (n=35)	4.1±1.8	2.8±2.2	2.7±2.4	3.5±2.2
Hip fracture (n=32)	3.5±2.2	0.9±0.9	1.0±1.0	2.1±2.0
Total (n=98)	4.1±1.9	2.4±2.2	1.8±1.9	3.2±2.2

ADL: Activities of Daily Living (0 to 6); Pre-morbid: 2 weeks before admission; *p-value <0.05 for comparisons between 3 groups (Wilcoxon rank sum test).

nificantly higher for hip fracture patients than for the other patients (75% *vs* 33%, $p<0.001$). Table 2 lists the comparison of functional evolution between the 3 subgroups. In univariate analyses of biological markers, IL-6 and IGF-1 were significantly different according to further functional decline. IL-6 levels were significantly higher in patients with hip fracture compared with the rest of the cohort (data not shown).

Multivariate analyses

Logistic regression was used to select two biomarkers: IL-6 and IGF-1. There was no correlation between these two parameters (Spearman rho=-0.16).

SHERPA, IL-6 and IGF-1 were thus included in a combined predictive model (SHERPA+). Areas under the ROC curve and their confidence intervals [95% CI] were 0.79 [0.69-0.86] for SHERPA+ *vs* 0.73 [0.63-0.81] for SHERPA alone ($p=0.14$) (Fig. 1). The logistic regression equation proposed for risk calculation is:

f = (SHERPA / 4) + (IL-6 / 250) + (IGF-1 / 125) – 0.45

Brier scores were 0.185 and 0.213 for SHERPA and SHERPA+ respectively, indicating a good predictive capacity within individual patients. Table 3 lists the calibration of both models: with SHERPA+, the mean predicted probability of functional decline was very close to the mean observed rate of decline within the four subgroups (determined by quartiles of estimated risk).

Since the risk of functional decline was higher in patients with hip fracture, we tested the predictive value of these biomarkers independently of disease status. When the SHERPA+ model was challenged by including the diagnosis "hip fracture", only SHERPA, IGF-1 and diagnosis were significantly associated with functional decline. However, in the subgroup of patients with hip fracture, IL-6 and IGF-1 were significantly associated with functional decline (p-values respectively 0.049 and 0.028).

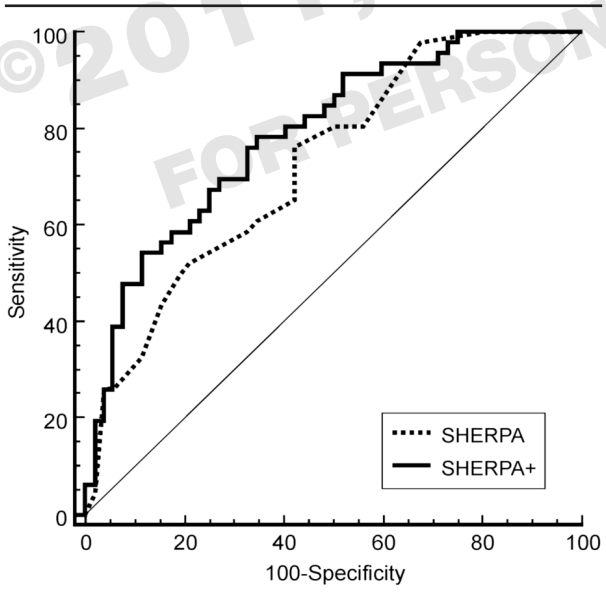

Fig. 1 - *Comparison of ROC for SHERPA and SHERPA+. SHERPA: Score Hospitalier d'Evaluation du Risque de la Perte d'Autonomie; SHERPA+: Logistic regression model including SHERPA, IL-6 and IGF-1; p-value for comparisons of AUC=0.14.*

DISCUSSION

In this population of acutely ill hospitalized elderly, the combination of proinflammatory and hormonal biomarkers (IL-6 and IGF-1) with a clinical screening tool (SHERPA) improved the accuracy of the prediction of functional decline 3 months after hospitalization, compared with SHERPA alone. Although the discriminative ability of SHERPA+ (area under the ROC curve) only marginally improved, the composite model had better calibration performance, since the proportion of patients who actually underwent functional decline matched the average predicted risk of functional decline within the defined subgroups. The added value of SHERPA+ to clinical prediction may be due to better stratification of patients at intermediate risk, as indicated by the calibration. The question remains as to whether IL-6 and IGF-1 are directly involved in the physiological pathway of functional decline, or whether they are simply markers of the comorbid process. In their hypothesized pathway to frailty, Walston et al. emphasized the central role played by IL-6 and IGF-1 in the impairment of various physiological systems, including muscle and the immune system (11). Bautmans et al. did show that higher levels of inflamma-

Table 3 - *Comparison of predicted risks and observed rates of functional decline.*

Subgroups	Probability of FD (%)	SHERPA			SHERPA + (IL-6 and IGF-1)		
		Patients (n)	Predicted FD rate (%)	Actual FD rate (%)	Patients (n)	Predicted FD rate (%)	Actual FD rate (%)
1	0-24	18	21	6	23	14	13
2	25-49	36	36	50	28	35	39
3	50-74	41	65	61	29	61	59
4	75-100	3	82	67	18	84	83

SHERPA: Score Hospitalier d'Evaluation du Risque de la Perte d'Autonomie; SHERPA+: SHERPA+IL-6 and IGF-1; FD: functional decline. Subgroups are based on quartiles of estimated risk of FD for SHERPA and SHERPA+ explaining why number of patients in subgroups vary; 4 categories were determined: 0 to 25%, 25% to <50%, 50% to <75%, 75% to 100%. Predicted FD rate is mean predicted risk per subgroups with logistic model; actual FD rate is mean rate of FD in each subgroup measured 3 months after discharge.

tion were associated with significantly worse muscle function in geriatric hospitalized patients (23), which may at least partly explain the functional impairment.

This study is one of the first addressing the potential of selected biomarkers to improve clinical prediction of functional prognoses for hospitalized elderly in unstable medical condition. Until now, biomarkers have mainly been associated with adverse functional outcomes in community-dwelling patients, and little research has been done in hospitalized elderly. In older patients hospitalized for pneumonia, El Solh et al. studied the potential association of inflammatory markers with functional recovery (24). In their cohort of 301 patients, TNF-alpha (but not CRP) was associated with functional loss at the time of hospital discharge. Inflammatory markers had no effect on functional recovery 3 months after discharge (24). Formiga et al. analysed serum IGF-1 levels in nonagenarian hospitalized patients (n=60) and found that the decline in ADL 3 months after discharge from hospital was not correlated with serum levels of IGF-1 on admission (25). Wu et al. proposed a mathematical model predicting functional decline 2 months after hospital discharge which included measurement of albumin (10). This is convergent with the fact that malnourished patients are more likely to present functional decline 3 months after discharge (26). However, our results did not confirm the influence of albumin.

There are several important limitations to these results. The 3 subgroups of patients differed significantly in their functional evolution. The predictive value of these biomarkers is not independent of disease status. Indeed, when admission diagnosis is included in the logistic regression model SHERPA+, only IGF-1 remains significantly associated with functional decline. Patients with hip fracture should be considered as at high risk of functional decline, and biomarkers have limited additional predictive value. Further studies are needed to confirm our results in a cohort representative of older patients admitted through the emergency department. Due to the selection of patients and the need for further validation, we do not provide a new scoring scale or a table listing the operational characteristics for various SHERPA+ cut-offs. The interaction between primary diagnosis, biomarkers and functional decline in this study is a limitation, and the contribution of the selected biomarkers to predict functional decline should be tested in larger groups with various acute disease conditions.

Another limitation is that our definition of functional decline does not allow identification of the time-frame in which patients develop this decline (before, during, or after hospitalization). However, these time-points have been used in other cohort studies (5, 6), and consider the event 'hospitalization' in a continuum of functional evolution. Long-term perspectives are important in older frail patients, since the impact of acute illness may become apparent only after hospital discharge (27). At this stage, the clinical application of SHERPA+ is limited. The two biomarkers are more expensive than clinical assessment with SHERPA and provide limited improvement of the prediction of risk. However, the association of high levels of IL-6 and low levels of IGF-1 is concordant with observations in community-dwelling patients.

Proper identification of frailty is a major public health issue in providing adapted care to vulnerable hospitalized elders. Clinical tools predicting functional decline, mainly based on physical or more comprehensive clinical criteria, have shown only moderate discriminative ability, and therefore inclusion of biological factors may improve performance, as in the estimation of cardiovascular risk (28). Further studies should include larger cohorts, and combine several biomarkers in composite indexes.

Another perspective is that persistent changes in inflammatory and endocrine markers may be better predictors of functional decline than baseline measures, as has been suggested in community-dwelling seniors (29), and as shown in older patients hospitalized for pneumonia that presented longer inflammatory activity compared with younger patients (30), and the kinetics of inflammation may be associated with functional reserves.

In conclusion, screening functional decline in hospitalized older patients may give an estimate of their frailty

level. Targeting at-risk patients early after admission is a prior issue, and selected biomarkers add limited predictive value to SHERPA scores.

ACKNOWLEDGEMENTS

We are grateful to Céline Divoy, MSc, Delphine Thimus Msc, Laurence Galanti, MD, PhD and Stéphanie Delieux for their technical or administrative contribution and for their scientific support to this study. This work is funded by the Walloon Region (Reseaux 2, RW 51/6193, SENEGENE). The sponsors had no role in study design, data collection, analysis, interpretation or presentation. The authors declare no conflict of interest.

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